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## Review article

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# Hereditary motor and sensory neuropathies

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The hereditary motor and sensory neuropathies (HMSN) represent a genetically heterogeneous collection of disorders in which patients develop a progressive muscular atrophy and sensory neuropathy of the distal extremities. Although Dyck<sup>1</sup> has noted seven types, the best described of these are HMSN types I and II (Charcot-Marie-Tooth disease) and Déjérine-Sottas (DS) disease, HMSN III. In contrast to other neurological disorders, such as Huntington's disease and myotonic dystrophy, there appears to be extensive genetic diversity in HMSN. The recent use of pedigree linkage analysis together with recombinant DNA techniques in these disorders has finally begun to clarify this confusing group of diseases.<sup>2-4</sup>

Charcot and Marie,<sup>5</sup> and independently Tooth,<sup>6</sup> described a hereditary progressive muscular atrophy of the lower extremities in 1886. The former authors suspected the disorder represented a myelopathy, while Tooth considered it to be a 'true neuropathy'. Today Charcot-Marie-Tooth (CMT) disease represents the most common inherited neuropathy, with estimates of 36/100 000<sup>7</sup> for the prevalence of its most frequent type, the autosomal dominant form. Presentation of symptoms is commonly in childhood or as a young adult. Initial weakness occurs in a peroneal nerve distribution with development of the characteristic foot drop, pes cavus, and hammer toes. Sensory examination is abnormal as well, but deficits are usually not symptomatic. The disease is progressive and atrophy of the distal upper extremities may occur in many subjects. Like many inherited neurological disorders, CMT is marked by variable expressivity. Some patients may have only minimal symptoms, and their diagnosis may rest on nerve conduction studies or obligate carrier status, while others may require extensive orthopaedic intervention to maintain ambulation. A few patients may become wheelchair dependent. Ataxia and especially intention tremor are not uncommon.<sup>8</sup> Prominence of these later symptoms led Roussy and Levy<sup>9</sup> to describe what was

initially believed to be a distinct syndrome. However, subsequent identification of families in which the CMT1 (HMSN I) and Roussy-Levy phenotypes segregate as one gene has led to the conclusion that patients with Roussy-Levy syndrome actually represent extreme expressions of CMT1.<sup>10</sup> With the known linkages to chromosomes 17 and 1 in CMT1, proof of this clinical impression may be obtained through future linkage analysis.

In 1968, Dyck and Lambert<sup>11 12</sup> divided the autosomal dominant forms of CMT into two types, based on physiological and pathological criteria: (1) the demyelinating form, CMT1, with severely decreased nerve conduction velocities (NCV) and hypertrophic changes on biopsy, and (2) CMT2, the neuronal form, with normal or mildly decreased NCV, and lacking the hypertrophic changes on biopsy. However, on an individual patient basis, these two types are clinically indistinguishable. Later, Thomas *et al*<sup>10</sup> introduced the term hereditary motor and sensory neuropathy for a group of peroneal atrophies including CMT and DS disorders. Later, Dyck<sup>1</sup> expanded this term to include CMT1 as HMSN I, CMT2 as HMSN II, and DS as HMSN III. Recently, this terminology has been somewhat confusing as genetics publications have tended to use the designation CMT1 and CMT2 while neurology publications have followed the HMSN designation. For clarity of this discussion, I will use CMT1 and CMT2 interchangeably with HMSN I and HMSN II respectively.

Herringham<sup>13</sup> in 1888 presented a family which raised the possibility of an X linked form of CMT. Later, Allan,<sup>14</sup> in reporting a large North Carolina family, also suggested the existence of such an X linked form. Several authors, however, believed these families not to be X linked but rather variable expression of the dominant form.<sup>15</sup> Indeed, the family of Herringham<sup>13</sup> did show male to male transmission. However, subsequent expansion of the original family of Allan<sup>14</sup> allowed Rozear *et al*<sup>16</sup> to show overwhelming evidence for X linkage (32 million:1). This was accompanied by establishment of linkage in this and several additional families to pericentromeric X chromosome markers.<sup>17</sup> X linked families have been demyelinating in type, with males expressing an

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increased severity of symptoms relative to female carriers. It seems likely that X linked dominant and recessive families are examples of variable expression within these families, rather than separate genetic entities themselves.<sup>18</sup>

Autosomal recessive families of CMT with adult or adolescent age of onset have been reported by several authors.<sup>15-19</sup> Supporting autosomal recessive inheritance in these families is the absence of signs or symptoms of CMT in those parents tested and increased consanguinity within these families together with the presence of multiple affected sibs. Studies of NCV have suggested that autosomal recessive forms of both demyelinating and axonal types exist.<sup>15</sup>

Age of onset in the dominant forms of CMT has been estimated to be 12 to 19 years in type 1<sup>20</sup> and believed to be slightly later in type 2. However, there is a wide range in age of onset, as well as clinical presentation. Indeed, asymptomatic gene carriers are known and many subjects may not express the disease until later in life. Therefore, the clinical penetrance of this disorder is not complete and is affected by age. However, electrical diagnosis in type 1 does not indicate such age of onset variability and a reasonable estimate of penetrance based on nerve conduction studies would appear to be 100%. Most gene carriers of type 1 will show decreased NCV (less than 60% of normal) by the age of 6 to 7 years,<sup>21</sup> often years before developing any symptoms.

HMSN type III<sup>22</sup> differs from the majority of CMT1 and 2 families, with mean age of onset occurring in infancy or early childhood. This early age of onset overlaps with CMT, as infantile cases of CMT type 1 are known to exist.<sup>23</sup> HMSN III follows an autosomal recessive pattern of inheritance and patients generally display an increased severity of symptoms. Pathologically, it is a hypertrophic neuropathy, sharing similar findings with CMT1. Ouvrier *et al.*<sup>23</sup> have studied several CMT1 and HMSN III patients and found the mean axon diameter/fibre diameter to be the only distinctly different pathological parameter, being large in HMSN III. However, this has recently been disputed.<sup>24</sup>

Clinically, HMSN III is marked by variable expression of symptoms similar to CMT1. Walking is frequently delayed and impaired in later life. Facial weakness is also common.<sup>22-23</sup> NCV are quite slow (usually below 12 m/sec), but overlap with values obtained in CMT1 families. Ataxia is very frequent and may be a major incapacitating symptom.

Whether HMSN III is indeed a unique disorder or an example of variable expressivity of CMT1 has been addressed by several authors.<sup>23-25</sup> Given the normal electrophysiology of parental nerves, it seems unlikely to be allelic to the autosomal dominant forms of CMT1. Whether it shares the same genetic locus as autosomal recessive CMT1 is unknown and currently would seem difficult to assess. Hopefully, linkage

analysis will be able to address this point in the future as well.

### Linkage studies

The ability to detect CMT1 gene carriers at an early age using nerve conduction studies makes the disorder particularly efficient for pedigree linkage analysis compared with late onset disorders like Huntington's disease or Alzheimer's disease. Bird *et al.*<sup>26</sup> initially suggested linkage of CMT to the Duffy blood group locus (*Fy*) in 1980, with a lod score of 2.30 at  $\theta=10$  cM. When Guiloff *et al.*<sup>27</sup> using two additional families, added a lod score of 0.725 to this total, a cumulative lod score of 3.025 was reached for this linkage group. Shortly thereafter, Stebbins and Conneally<sup>28</sup> reported a lod score of 3.11 in an independent Indiana family. This raised the expectations of a similar linkage to chromosome 1 in all CMT1 families. However, later studies<sup>29-31</sup> soon showed that this linkage was far from consistent. With an increasing number of families excluding linkage to chromosome 1, Bird *et al.*<sup>29</sup> suggested the non-Duffy linked types be termed HMSN Ia (CMT1a), while those linked to *Fy* be classified as type 1b. Over the next few years, confusion arose over the degree of genetic heterogeneity in type 1, and in particular the percentage of families actually linked to the *Fy* locus. In retrospect, this confusion appeared to have arisen from several factors. (1) The *Fy* locus is a relatively uninformative marker for linkage analysis and many families used in the linkage analyses were not of sufficient size to be classified as linked or unlinked with reasonable confidence. In addition, it has only recently been mapped to a defined region (1q21.1-1q23.3)<sup>3</sup> and, as such, few polymorphic DNA markers were available for confirmatory studies. (2) Interpretation of positive lod scores for individual families, in the presence of known genetic heterogeneity, can often be misleading. Small positive lod scores can occur from any family, no matter what is their true linkage status. Therefore, when known genetic heterogeneity exists, it is important to obtain some insight concerning which of these lod scores is significant. We usually accept linkage when a lod score is greater than 3.0 within a family,<sup>32</sup> but if the lod score value is less than 3.0, what are the chances of that family being linked to the marker locus?

First, for the locus in question, one can estimate the prior probability of linkage for any one family. This represents the estimated proportion of families known to be linked to that same locus in the population studied. The posterior probability of linkage is this value weighted by the obtained lod score for that family. This problem has been discussed by Ott<sup>33</sup> in detail, with particular reference to CMT. The posterior probability can be calculated by hand, or by using the program HOMOG, written by Ott.<sup>33</sup>

In analysing the CMT1 families, the proportion of families with actual *Fy* linkage was unknown. The failure to deal correctly with this inherent problem of heterogeneity led to the suggestion of *Fy* linkage in several families, with only moderately positive scores.<sup>34</sup> Conversely, those with similarly negative scores were grouped as unlinked.<sup>35</sup> In retrospect, with subsequent data (see below), many of these small positive scores might have been secondary to chance and not, in fact, indicative of linkage to the *Fy* locus.

As it became increasingly clear that a substantial proportion of families (type 1a) were not linked to chromosome 1, general screening of these families began. In 1989 we reported finding four type 1a families from Duke University, along with two large type 1a families from the University of Sydney, linked to two chromosome 17 markers, *D17S58* and *D17S71*, in the pericentromeric region of the p arm.<sup>2</sup> This has since been confirmed by other investigators.<sup>36-37</sup> In reviewing the CMT1 families presently tested, it now appears that the substantial majority of these CMT1 families are linked to chromosome 17. Now, the designation CMT1a (HMSN Ia) no longer represents non-Duffy linked families, but rather families linked to chromosome 17.

Included in a recent report by Middleton-Price *et al*<sup>36</sup> are the two families used in the initial CMT-*Fy* linkage by Guiloff *et al*.<sup>27</sup> Interestingly, while only one family was informative for the markers reported, the lod score was 1.65 for *D17S71* in that family.

Chance *et al*<sup>6</sup> have proposed the existence of a third type of CMT1 (1c?). The authors reported that one of their seven families excluded linkage to both *Fy* and *D17S71* at 5 and 10 cM respectively. If this exclusion is confirmed, then a third autosomal dominant locus may exist for this already heterogeneous disorder.

At present only the original family of Stebbins and Conneally<sup>28</sup> has shown significant linkage to chromosome 1, although others have suggestive lod scores. This family has also shown linkage to the IgG receptor FCgammaRII.<sup>4</sup> Mapping estimates place this locus approximately 6 cM from the *Fy* locus. Unfortunately, the initial family of Bird *et al*,<sup>26</sup> with suggested *Fy* linkage, has not yet proven to be informative for this marker, but has been excluded from the chromosome 17 region. Therefore, at present, it is still likely to be a CMT1b (HMSN Ib) family. Lebo *et al*<sup>3</sup> have suggested that FCgammaRII may be a candidate gene for CMT1b, as no crossovers have been found between it and the CMT1b locus. However, with limited family data, the confidence limits for gene localisation are large and this gene may lie within a fairly large region. In fact, localisation may be quite difficult with only one family, without a physical marker (translocation, deletion) to aid in identification of a small region to be screened for an abnormality.

Recently, we have sublocalised the CMT1a gene to 17p11.2, using multipoint linkage analysis.<sup>38</sup> It is

probably flanked by the markers *D17S122* and *D17S124*. Currently, an international linkage consortium of several centres is under way to try and provide additional localisation within this region.

Relatively fewer linkage studies have been performed in CMT2. This may reflect, in part, the greater difficulty in diagnosis of these patients and gene carriers. In addition, there is a suspicion among many clinicians that CMT2 may be more heterogeneous than CMT1, as clinical variability between CMT2 families appears greater than between families of type 1. Families with intermediate NCV (greater than expected for type 1 but less than for type 2) have also been reported.<sup>39</sup> Whether these are unique loci or represent the spectrum of clinical variability is one of the interesting questions to be clarified in the future.

Ionasescu *et al*<sup>40</sup> reported a lod score of 1.24 with serum amyloid P component in three CMT2 families. But recently Loprest *et al*<sup>41</sup> excluded linkage to this marker and the region surrounding the chromosome 17 markers *D17S58* and *D17S71* in one large CMT2 family. Analysis in this family with FCgamma RII is currently under way. However, considering the pathological and physiological differences between these two disorders, it is expected that the CMT2 locus will not be allelic to CMT1. Finally, linkage analysis of several X linked families have been reported.<sup>18</sup> The sublocalisation of the gene is currently not clear, but it appears to lie near the centromere, most likely on Xq. Further sublocalisation has not yet been done.

### Animal models

At present, the best possibility for an animal model is the trembler mouse (*Tr*). Inherited as an autosomal dominant trait, affected animals develop a hypomyelinating neuropathy with onion bulb formation in older animals.<sup>1</sup> However, the most intriguing reason to consider *Tr* as a possible model for CMT1a is its location on mouse chromosome 11, near the homologous region for distal human chromosome 17p.<sup>42</sup> It is not yet known if this region extends to include *Tr*. If it does, this would strengthen the case for *Tr* as a mouse model, and would suggest that a common genetic aetiology may be shared with CMT1.

### Genetic counselling

As with any common symptom like neuropathy, non-genetic aetiologies should be ruled out in the initial study of an isolated patient. Study of a subject at risk for type 1 must include nerve conduction studies, as asymptomatic gene carriers with normal neurological examinations are known to exist. In sporadic cases, NCV on both parents should also be obtained if possible. At present, no obligate gene carriers with CMT1 have been identified with normal NCV. Nerve

biopsies may be useful, but are generally not specific. While linkage analysis will eventually allow gene carriers to be identified, the degree of heterogeneity and the marker distances involved do not allow use of these markers at present. In addition, differentiation of autosomal versus X linked forms may be difficult, especially in small families, where the opportunity for male to male transmission may be low.

When close markers for carrier detection do become available, the calculation of posterior probabilities of linkage through HOMOG may be needed for large families with CMT1 in which appreciable lod scores can be obtained.

### Conclusion

The inherited group of peroneal atrophies have undergone continual classification as more powerful investigative tools have become available. Now we begin to approach the final level in this process, delineation of the actual defective gene. As the term peroneal atrophy has become superseded, so may the classification of hereditary motor and sensory neuropathies, with the future identification of these defects. Hopefully, the elucidation of these genes will provide insight and understanding not only of each unique disorder, but of the complex process of peripheral nerve function as well.

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